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New Treatments for Macular degeneration -

Information for General Practitioners and Optometrists.

Background:

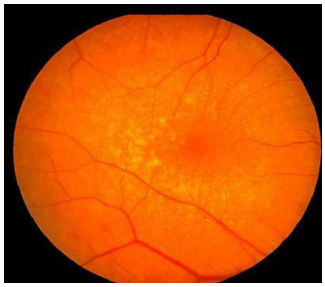
The last 24 months has seen a flurry of new treatments for wet macular degeneration (AMD). Several drug trial results were released in 2005 and one was given FDA approval. However in the latter part of 2005 a clear front-runner was established which will shape the future of AMD treatment. Laser treatments such as Argon laser photocoagulation, and photodynamic therapy (PDT), and transpupillary thermotherapy will give way to new anti-angiogenic therapy such as Macugen, Lucentis and Avastin.

I will start by describing how CNV is classified and its natural history as this impacts our understanding of drug trial data, I will assess the current situation and summarize the next generation of treatments for AMD.

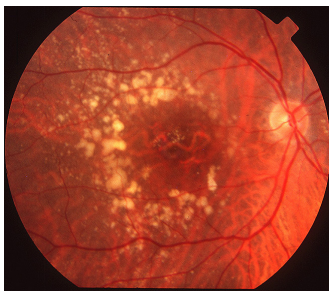
The Classification of Age related maculopathy (ARM):

ARM is a degenerative condition of the macula, characterized by soft drusen, hard drusen and areas of hypo- or hyper-pigmentation, in patients >50 years of age. ARM is divided in to early and late forms, depending on visual acuity (<6/12 cut-off). Age related macular degeneration (AMD) is synonymous with late ARM. AMD is further divided into dry (geographic) and wet forms, the wet form being caused by choroidal neovascular membranes (CNV).[1]

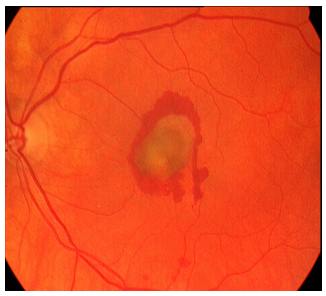
Stage II ARM



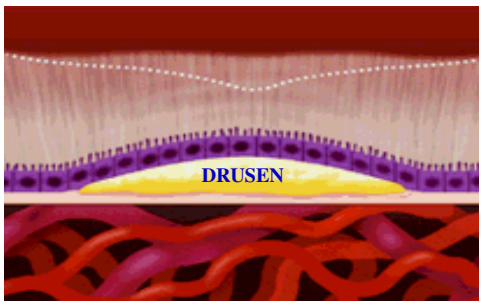
Dry AMD (Geographic)



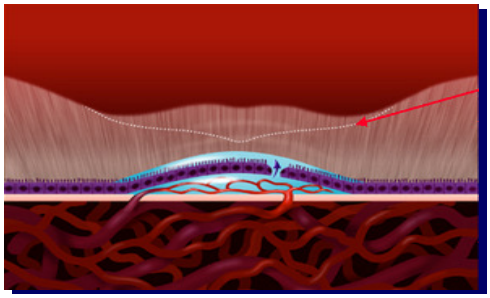
Wet AMD (CNV)



CNV are formed by a growth of blood vessels from the choroid, through gaps in Bruck's membrane, and lie under the retinal pigment epithelium (RPE). The blood vessels are stimulated to grow, by vascular endothelial growth factor (VEGF), released by the relative ischaemia of the retina / pigment epithelium.[2]



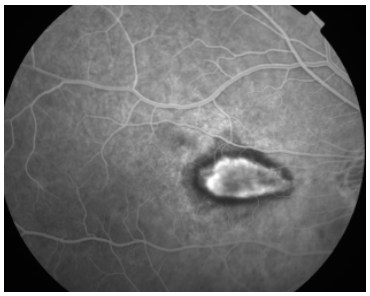
Lipid deposition in Burch's membrane renders the RPE ischaemic



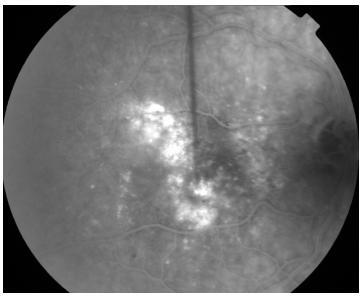
New blood vessels grow under the RPE

Classification of CNV

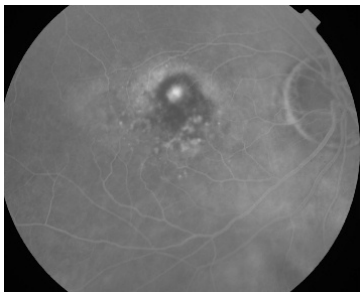
CNV are categorised by fluorescein angiography, into to classic (20%), and occult (40%), and mixed CNV (40%). Lesions with significant Classic components seem to cause more blindness.[3]



Classic- CNV (discrete leakage)



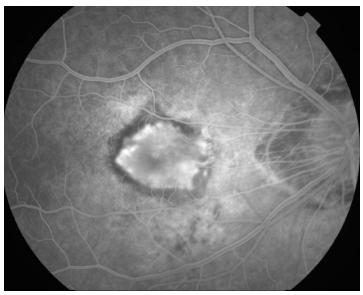
Occult-CNV (diffuse leakage)



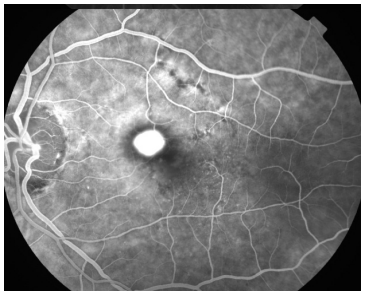
Mixed-CNV ..

classic CNV are also classified by their position in relation to the fovea. extra-foveal (>200µm), juxta-foveal, (0-200 µm) sub-foveal, and peri-papillary. Treatments vary for the position of CNV, as well as the type of CNV.

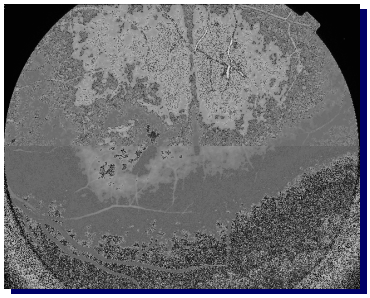
Categorisation of Chorodial neovascularisation



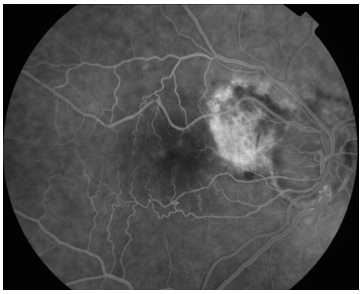
Sub-foveal CNV



Juxta-foveal CNV



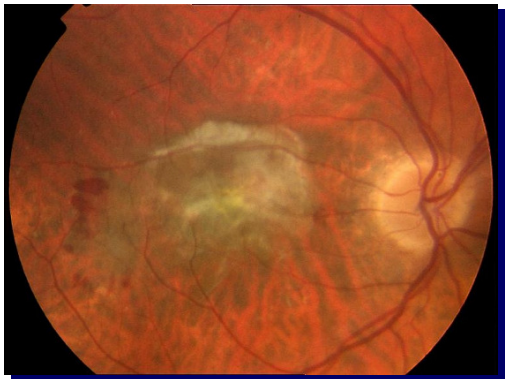
Extra-foveal CNV



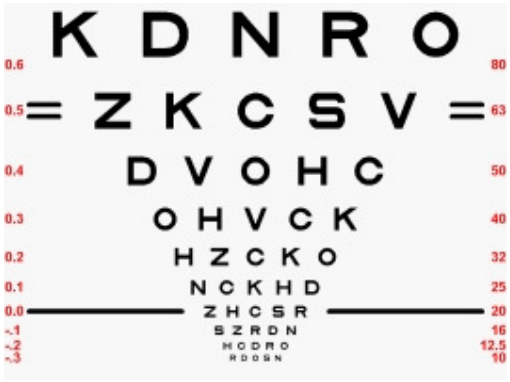
Peri-papillary

Natural History of Choroidal neovascularisation

Without treatment most patients with CNV will go on to develop a disciform scar, causing severe central visual loss. Despite treatments AMD is the commonest cause of blindness in the UK, with over 16,000 registrations per year, and perhaps a further 30,000, non-registered patients, loosing vision. Treatments have focused on CNV, which accounts for around of 50% of patients with severe visual loss. The treatment outcomes are measured in terms of recurrence of CVN, the number of LogMAR letters lost and the proportion of patients suffering moderate visual loss (MVL). MVL is the doubling of the visual angle, equivalent to; loss of 3 lines on LogMAR chart, or 15 LogMAR letters; Severe visual loss (SVL), is quadrupling of the visual angle equivalent to: loss of 6 lines on ETDRS chart, or 30 LogMAR letters.



Disciform scar, pale sub-retinal scaring the end stage of CNV



LogMAR visual acuity chart (Snellen equivalent on Right)

In general all treatments are only offered for patients with active lesions, and visual symptoms, as the laser treatments carry a risk of CNV re-activation, and intra ocular injections of infection, retinal detachment and cataract.

Current treatments

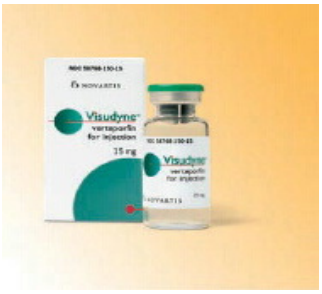
Argon Laser: This is reserved for extra-foveal CNV which present rarely (2-5% of all CNV), patients are relatively asymptomatic, until the CNV is sub-foveal. As the lesions lie away form the fovea, argon laser photocoagulation may be used without loss of central vision. Data from the Macular Photocoagulation Study (1991) showed found that 46% of the treatment group vs. 64% of the control group had severe visual loss at 5 years. Most clinicians would use this treatment sparingly, as laser burns can spread throught the fovea, and recurrences are common (50%).[4]

Argon laser can also be used for patients with an active peri-papillary CNV, leakage under the fovea has occurred, and vision has been lost. Other treatments include diode laser or sub-retinal surgery may be most appropriate. The outcomes of these lesions tend to be variable however if leakage can be stopped patients can have a satisfactory (2-3 line) gain in vision, as the fovea is unaffected.

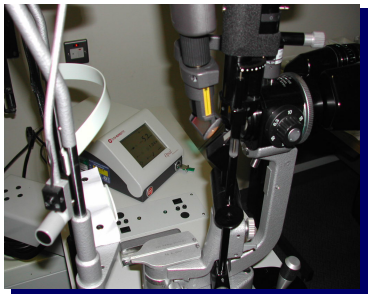
Verteporfin (Novartis)

Treatment with this photoactive dye has largely been replaced with anti-VEGF injections that give better visual results. However I will give a brief description as sometimes joint therapy works well. The most widely used is photodynamic therapy with Verteporfin. Verteporfin is a photoactive dye, that when injected binds to low density lipoproteins, this complex is taken up by the choroidal new vessels. The dye is injected over 10 minutes and a low power laser (689nm) is used to activate the dye. This generates free radicals and singlet oxygen which cause damage to the blood vessels and close the abnormal vessels. [5]

The laser spot sizes are typically large between 2-5mm, and the retina is treated for 83s. Typically this is a pain fee treatment, tolerated well by the patients, several notice a drop in vision for 24-48 hours which then recovers, to a pre-operative level. Treatment is typically given three times in the first year, twice in the second and 1-2 times in the third.



Visudyne

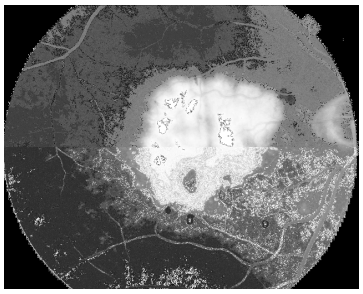


PDT laser, mounted on a slit lamp

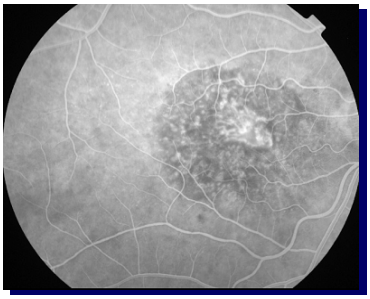
The key trials of Visudyne were the 'treatment of age related macular degeneration with photodynamic therapy' (TAP, 2001)[5] and 'Verteporfin in photodynamic therapy' (VIP, 2001)[6] trials. These were randomized controlled trials comparing PDT with controls in patients with CNV due to AMD. They assess the percentage of patients with stable vision at two years, defined by the loss of <3 lines of LogMAR vision.

Pure classic did best with 70% stability vs. 30% stability in the control group. Predominantly classic, did less well with only 59% stability, minimally classic did worse at 48% stability.[5] Patients with pure occult patients had 45% stability, compared with 32% of controls. However later in 2001, the data was re-analyzed to show that smaller occult lesions were found to benefit from PDT therapy. This led the retina journal to publish recommendations in 2002 that treatment should be considered for patients with: '*lesion size < 4 disc areas for*

AMD patients with either a minimally classic lesion composition or occult with no classic lesions'[7]

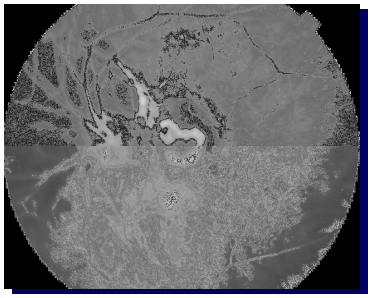


Pre PDT Treatment
VA 6/36

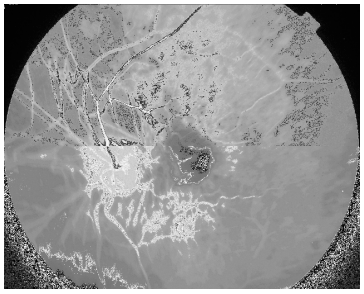


6m Post PDT treatment
VA 6/36

In the UK NICE evaluated the results of this these trials and issued guidance September 2003. Each treatment can cost between £1400-2100; secondly PDT is only moderately effective and for most patients vision does not improve, and for some it is lost. The photoactive dye does, effect other structures in the eye, and post laser there is a rapid increase in retinal inflammation for a few days, that can reduce the vision, in some occult lesions there is a 4% incidence of permanent visual loss and there are reports of the retinal pigment epithelium rips post treatment.



Pre: PDT / IVTA
VA 6/24



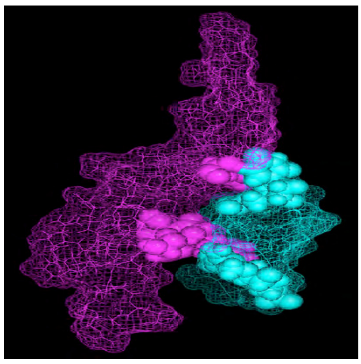
3m Post PDT / IVTA
VA 6/9

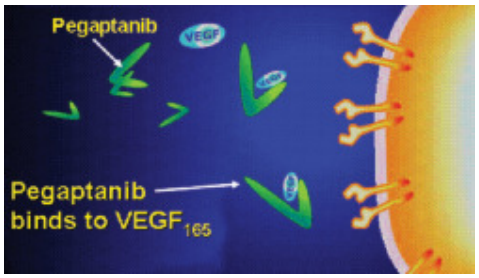
Non Laser treatments:

In 2005 non-laser based treatments began to make their mark, the main players in this field are currently, Macugen (pegaptanib sodium), Lucentis (ranibizumab), and Avastin (bevacizumab).

Pegaptanib sodium (Macugen):

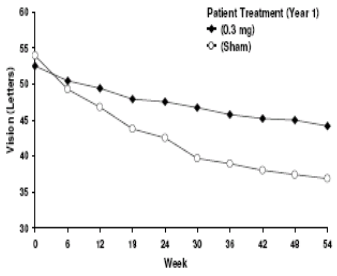
Macugen is an RNA analogue (pegalated oligonucleotide) that binds to $VEGF_{165}$ receptors on the cell surface, it reduces the leakage and sub-retinal haemorrhage from CNV. Macugen is injected into the eye on a 6 weekly basis.[9]

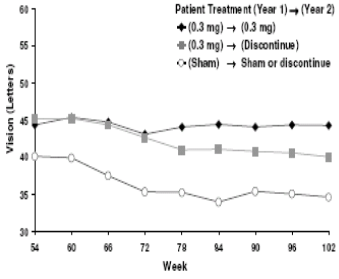




Macugen Binds $VEGF_{165}$

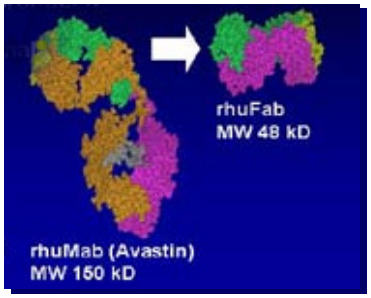
Early trials with Macugen 0.3mg, showed stable vision at one year (=/- 3 ETDRS lines) in Macugen 75% vs. Sham 60%. PDT was used in 27% of sham patients and 20% of Macugen patients. In two years an average of seven LogMAR letters were lost. These data were similar or slightly better than those from the PDT trials. However clinicians are concerned of the infection risk of multiple treatments, and also some patients had significant membrane reactivation following cessation of treatment.

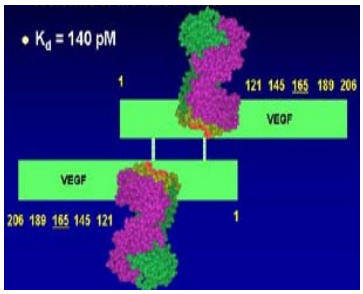




Lucentis (Novartis)

Lucentis is a humanized mouse monoclonal antibody to all isoforms of VEGF and made a big impression in 2005, with two very positive trial reports.[11] The FOCUS and MARINA. Again the drugs are injected at monthly or 6 weekly intervals and reduce macular fluid in the majority of cases.



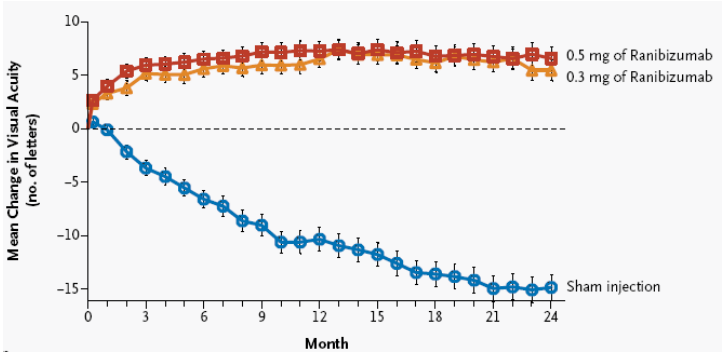


Lucentis rhuFab,

Binds to all VEFG isoforms

Data from MARINA, a Phase III clinical study of 716 patients with minimally classic or occult wet AMD, show that, at 12 months, approximately 95% patients treated with Lucentis maintained or improved vision (loss of <15 LogMAR letters), in both the 0.3 mg (94.5%) or 0.5 mg (94.6%), compared with 62.2% in the control group (p<0.0001).

Vision improved > 15 letters in 24.8% of patients with 0.3 mg of Lucentis and 33.8% of patients treated with 0.5 mg compared to 4.6% in the control group (p<0.0001). At 12 months, patients treated with Lucentis experienced an increase of seven letters in LogMAR visual acuity, while patients in the control group experienced a mean decrease of 10.5 letters (p<0.0001).

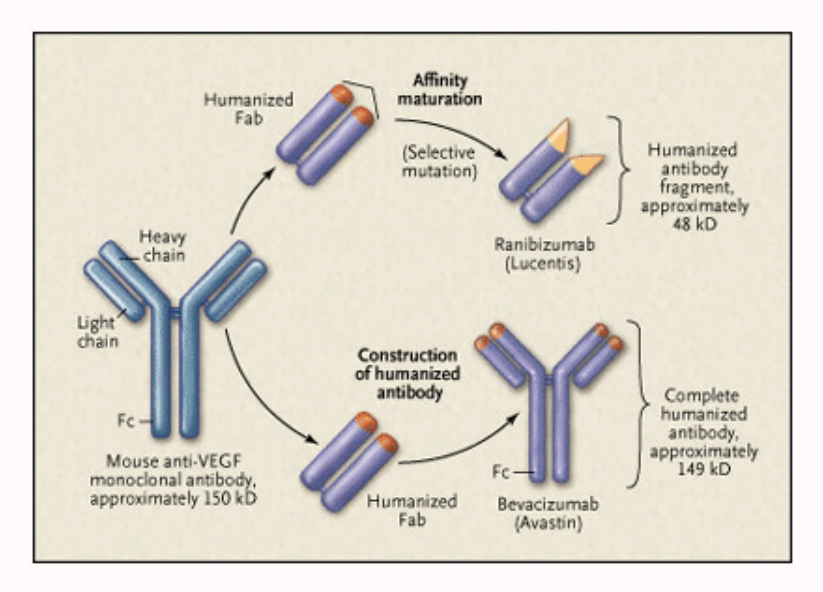


Vision Data from the MARINA study, the red lines are patients treated with Lucentis, gaining vision, and keeping it over 24 months.

These are startling results and pave the way for a new generation of treatments of AMD. By improving the vision Lucentis has raised the bar in terms of treatment efficacy for patients with AMD.

We know that VEGF plays a key role in the pathogenesis of other disease such as diabetic maculopathy and central retinal vein occlusion, so Lucentis may be of use in all these conditions, and trials into other retino-vascular diseases are currently running.

Lucentis will almost certainly be the gold standard drug for AMD treatment by the end of 2007, and passed through NICE by 2009.



Bevacizmaub (Avastin- Genentech):

Avastin is a humanized mouse monoclonal antibody, to VEGF, the molecule is slightly larger than Lucentis, it is currently licensed for use in patients with bowel cancer. Initial trials have used intravenous[12] and intravitreal dosage.[13] It is injected into the eye 4-12 weekly depending on the activity of the CNV.

The results for this treatment are similar to Lucentis. A recent publication in Ophthalmology by Avery et al looked at 81 eyes of 79 patients with monthly Avastin injections for 3 months. There ere few side effects and the vision improved from 20/200, to 20/125, with resolution of

the CNV. There were no particular safety issues apart from those associated with intraocular injections.

The forthcoming ARVO (2007) conference has over 140 presentations on the cell biology and clinical use of Avastin demonstrating the intense international interest in the compound.

These can be broadly be divided into those which deal with safety, those dealing with visual outcomes of CNV, and those dealing with other conditions such as CRVO, BRVO, Diabetic retinopathy, and other conditions such as Von Hipple Lindau. The reasons that these conditions have been looked at is that they are also based around abnormal secretion of VEGF, inducing both leakage and neovascularisation, as a response to retinal ischaemia.

A head to head trial of Avastin against Lucentis is planned, and there have been calls for Avastin to be trialled for other retinal conditions eg diabetic maculopathy.

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